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(54) PREPARATION FOR TREATING FLUID-DISCHARGING
 SKIN SURFACES, WOUNDS, SORES AND
 MUCOUS MEMBRANES

(71) We, PHARMACIA AKTIE-
BOLAG a Swedish Company, of Rapskatan
 7, Uppsala, Sweden, do hereby declare the
 invention, for which we pray that a patent
 may be granted to us, and the method by
 which is to be performed, to be particu-
 larly described in and by the following state-
 ment:—

The present invention relates to a method
 for treating fluid-discharging skin surfaces,
 wounds, sores, and mucous membranes, and
 to means for carrying out the method.

Previous proposals have been made to use
 liquid-absorbing materials in conjunction
 with liquid-discharging skin surfaces. Accord-
 ing to one method, the material is a wound
 dressing, which is placed over the liquid-dis-
 charging skin surface and itself absorbs the
 liquid.

The aqueous liquid which is discharged
 from a wound may contain, *inter alia*,
 fibrinogen and degradation products of
 fibrinogen, so-called split products. In the
 last stage of blood coagulation, thrombin
 converts the fibrinogen enzymatically to
 fibrin monomers, which latter, by a cross-
 linking reaction, promote the formation of
 scar. However, it has proved to be disad-
 vantageous if such scar is formed on a liquid-
 discharging skin surface. The scar forms a
 barrier capable of preventing the transporta-
 tion out of the wound of dirt, bacteria, toxic
 degradation products and other substances
 which are detrimental to the healing process.
 Cleansing of the wound and subsequent heal-
 ing thereof is thereby unfavourably affected.

It has now been found that it is important
 to have a low concentration of fibrin mono-
 mers and crosslinked fibrin immediately ad-
 jacent to the discharging surface, if the sur-
 face is to become effectively clean. The
 Applicants have discovered that the concen-
 tration of fibrin monomers and the cross-
 linked fibrin on the actual liquid discharging
 surface can be so controlled that subsequent
 reactions, i.e. the scar formation, do not take
 place on the liquid discharging surface itself
 but at a distance therefrom.

The present invention provides a prepara-
 tion for treating a fluid-discharging skin sur-
 face, wound, sore or mucous membrane
 which comprises substantially dry particles of
 a water-insoluble hydrophilic macromolecular
 material capable of undergoing limited swell-
 ing in the fluid to form discrete gel par-
 ticles, the swellability of the macromolecular
 material being such that the particles can
 absorb low molecular weight constituents of
 blood plasma but cannot absorb to any
 material extent fibrinogen or other substances
 of the same or higher molecular weight, in
 admixture or conjunction with a dermato-
 logically suitable carrier. It should be under-
 stood that the preparation of the invention
 may be used for treating any rupture of the
 skin surface, whether external or internal,
 from which there is a discharge. The pre-
 paration of the invention may be used for
 treating humans or animals; the animals may
 be commercially reared animals.

The invention also provides a pack for
 treating a fluid-discharging skin surface,
 wound, sore or mucous membrane, which
 comprises a container or package containing
 substantially dry particles of a water-insoluble
 hydrophilic macromolecular material capable
 of undergoing limited swelling in the fluid to
 form discrete gel particles, the swellability of
 the macromolecular material being such that
 the particles can absorb low molecular weight
 constituents of blood plasma, but cannot to
 any material extent absorb fibrinogen or other
 substances of the same or higher molecular
 weight, and also containing one or more pro-
 tective layers for retaining the macromole-
 cular material when applied to a wound.

In addition to low molecular weight salts,
 for example NaCl, KCl and CaCl₂, and amino
 acids, urea and glucose, the low molecular
 weight constituents of blood plasma include
 the so-called thrombocyte factors which in-
 fluence the first phase of the blood coagula-
 tion process. Examples of such low molecular
 weight active substances include prostaglan-
 dins, serotonin, adrenaline, adenosine di-
 phosphate (ADP), certain exo- and endo-

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try
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toxins having hydrolytic properties and divalent cations such as calcium or magnesium.

In accordance with one embodiment of the invention, the macromolecular material may be such that high molecular weight degradation products of the fibrinogen, for example those having a molecular weight of over 270,000, preferably over 165,000, and possibly also those having a molecular weight of over 85,000, or even those having a molecular weight of over 50,000, are completely or partly excluded from the particles. In accordance with another embodiment of the invention, the macromolecular material may be such that, in addition to the low molecular weight constituents of blood plasma, also substances having larger molecular weights (although smaller than fibrinogen) are permitted to penetrate completely or partially into the water-swollen particles. Examples of such relatively low molecular weight substances are relatively low molecular weight proteins and polypeptides, for example those having a low molecular weight in the region of up to approximately 5,000, or up to approximately 20,000 or, in certain instances, up to approximately 40,000.

The macromolecular material is selected so that particles thereof in a water-swollen state could be used in a column for conventional gel filtration purposes, thereby making possible, by means of gel filtration techniques, the complete or partial separation of molecules of, for example, the size of fibrinogen from small or smaller molecules of the aforementioned type. The cleansing effect according to the invention may be achieved in a particularly favourable manner by selecting particles of macromolecular material having the afore-mentioned properties, the water-swollen macromolecular material comprising a three-dimensional network.

The favourable result obtained when cleansing discharging skin surfaces using dry particles in accordance with the invention is thought to depend on a combination of several different effects. The dry particles initially absorb liquid between the particles by a capillary action and the extent to which this occurs depends on the space between the particles, and thus, when spherical particles are used, on the radius of the particles. A liquid migration from the surface of the wound through the particle layer is thus obtained at the same time as the swelling of the particles takes place. Simultaneously, a partition chromatographic effect is also obtained, since the low molecular weight constituents of the liquid are distributed both within and outside of the swollen particles depending on the molecular sizes, while the larger molecules for example fibrinogen, and, in accordance with some embodiments of the invention, the large molecular weight split products (degradation products) are unable to

penetrate the same. The substances excluded from the particles migrate towards the outer layer of the particle mass while progressively being concentrated, although this takes place under slight or controllable changes in ion strength or pH. This means that the participation of the fibrinogen in the formation of scar takes place in a zone remote from the discharging surface, instead of directly on said surface. The content of fibrinogen split products can also be increased by means of the afore-mentioned concentration effect. The split products represent active components in the coagulation process, because they prevent the polymerisation of fibrin, which leads to the formation of a defective fibrin coagulum or to no fibrin coagulum at all, and prevent the first phase of the blood coagulation of the fibrinogen degradation products, the so-called plasma thromboplastin formation phase. The coagulation phase, and therewith the scar formation, has in this way been modified and/or stopped by the formed gel and coagulation no longer takes place directly on the discharging surface, but is moved to a zone remote therefrom. This zone can readily be removed together with the gel particles, when these are removed. Cleansing of the discharging surface is facilitated by keeping the discharging surface free from such coagulation, thereby also facilitating granulation development. This greatly facilitates the later natural wound healing.

An important effect which may be obtained when using the particles according to the invention is that bacteria (and also small particles of dirt) are entrained with the liquid departing from the discharging surface to a zone where they do not affect said surface and where they later on may be readily removed together with the gel particles. By means of such separation effects, the growth of bacteria may be inhibited, because the medium surrounding the bacteria has been changed. The gel grains may also absorb nasty-smelling low molecular weight degradation products from bacteria, so that the smell from patients suffering from, for example, discharging leg sores and bed sores need not cause the other patients and the nursing personnel as great a discomfort as it does at present. Another important advantage obtained when using the particles according to the invention is that the particles are generally soft and will not adhere to the surface of the sore, even when saturated with fluid from the discharging surface, thereby enabling the particles to be removed painlessly. The gel formed can be readily removed by means of a spatula or may be washed away with a physiological saline solution.

Some types of the dry particles of macromolecular material which may be used in accordance with the present invention are

Fibrinogen mw 340,000

known *per se*, for example particles such as those obtained by the crosslinking of dextran or carboxymethyldextran with epichlorohydrin. These particles, however, have not previously been used for cleansing discharging skin surfaces, wounds and mucous membranes. A proposal has been made to incorporate some of these known particles in a water-swollen state, together with other components, in dermatological compositions for other purposes. These water-swollen particles, however, do not give a cleansing effect according to the present invention, which requires the particles to be substantially dry when applied to the surface to be treated, so that the necessary migration of fluid in the particle layer may take place.

Dermatological compositions which contain different types of dry particles have been previously proposed. Particles of polymeric substances have also been mentioned in this respect, although the particles have been of quite different types than the macromolecular materials used in the present invention. The particularly favourable cleansing effect obtained in accordance with the present invention is not obtained with these previously proposed compositions containing dry particles.

In accordance with the invention, the water-insoluble hydrophilic macromolecular material capable of undergoing limited swelling to form a gel may contain hydroxyl groups; these groups impart the important hydrophilic property to the macromolecular material. The hydrophilic properties of the macromolecular material may also be obtained by means of carboxyl groups, which are preferably present in the form of a physiologically tolerable salt. A carboxyl group-containing macromolecular material where the carboxyl groups may optionally be converted into salt form with, for example, a physiologically tolerable amine, may be suitable for cleansing fluid-discharging skin surfaces, which, for example, have arisen when the skin has come into contact with alkaline substances such, for example, as alkali metal hydroxides. In addition, or alternatively, the macromolecular material may contain amino groups and/or sulphonic acid groups, each of which is preferably in the form of physiologically tolerable salts, for imparting the necessary hydrophilic property to the macromolecular material. Macromolecular materials having carboxyl groups and/or sulphonic acid groups and/or amino groups may also affect the coagulation of the plasma emitted from a sore surface, thereby further delaying or preventing the formation of fibrin.

In accordance with the invention, the hydrophilic property of the macromolecular material is advantageously such that 1 g of the dry material, when swelling in the presence of water, absorbs at least 0.5 g, pre-

ferably at least 1 g, of water. On the other hand, the swellability of the material should not be so high that the material absorbs too much water. As mentioned above the swellability of the material should be such that the low molecular weight constituents of blood plasma, but not molecules of the size of fibrinogen, are able to penetrate the material. In general, 1 g of the dry macromolecular material should absorb less than 30 g, preferably less than 25 g (advantageously less than 20 g and especially, less than 15 g) of water. If the gel-forming particles used in accordance with the invention comprise, for example, dextran or carboxymethyl-dextran or starch or hydroxyethyl starch crosslinked by means of epichlorohydrin in alkaline aqueous solution to a water-insoluble but swellable three-dimensional network, a particularly good result is obtained if the degree of crosslinking corresponds to a water absorption ability of approximately 1.5 to 10 g, advantageously approximately 2 to 5 g, of water per gram of dry macromolecular material.

In accordance with a preferred embodiment of the invention, the macromolecular material is selected so that it has a high swelling rate when it comes into contact with water or with the aqueous fluid on the skin surface to be treated. The particles should normally absorb water and swell at a rate which is sufficiently high that fibrin and fibrin coagulum cannot be formed by the influence of the enzyme thrombin etc. in the zone adjacent to the discharging surface. Since fibrin is formed at different rates with different people there is conveniently selected a swelling rate for the particles which is sufficiently high for use with people having a high rate of fibrin formation. A good swelling rate is obtained by the presence of many hydroxyl groups in a three-dimensional network. A particularly high swelling rate is obtained by the presence of ionizable groups in the network, for example carboxyl groups, sulphonic acid groups and amino groups, any or all of which groups may be in the form of salt. As an example of good swelling rate (caused by the presence of, for example, groups selected from hydroxyl groups, carboxyl groups in sodium salt form, and sulphonic acid groups in sodium salt form (in, for example, crosslinked polymers obtained by for example crosslinking dextran or carboxymethyl-dextran or starch or starch derivatives with epichlorohydrin in alkaline aqueous solution)) one may mention a swelling rate in physiological saline solution or in water which is such that 1 gram of the dry particles of macromolecular material absorbs in 5 seconds more than 0.02, preferably more than 0.1, advantageously more than 0.2, and especially more than 0.5 g of water. The preferred upper limit on the amount of water absorbed under the above

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don't allow clot formation

conditions is 5 g, more especially 3 g, and, in particular 2 g.

In accordance with a particularly preferred embodiment of the invention, the water-insoluble hydrophilic material capable of undergoing limited swelling to form a gel comprises a three-dimensional network held together by bonds of a covalent nature. Thus, for example, the macromolecular material may comprise a hydroxyl group-containing three-dimensional network held together by bonds of a covalent nature, the network comprising hydroxyl group-containing macromolecules crosslinked by means of bridges connected to said polymer molecules by ether bonds. The bridges may be straight or branched aliphatic saturated hydrocarbon chains substituted by one or more hydroxyl groups and containing 3 to 20 carbon atoms, preferably 3 to 10 carbon atoms, said chains being optionally interrupted by one or more oxygen atoms. The product is insoluble, but swellable in water to form a gel, said gel in a fully water-swollen state advantageously containing more than 30, preferably more than 50, especially more than 60% by weight of water and less than 97, preferably less than 95, especially less than 90% by weight of water. When the crosslinked product contains hydroxyl-groups and/or carboxyl groups and/or sulphonic acid groups and/or amino groups, said groups may make up more than 5, preferably more than 10, advantageously more than 20% by weight and less than 60, preferably less than 50, advantageously less than 40% by weight of the dry particles. In accordance with the invention, the crosslinked macromolecules containing hydroxyl groups may be polymeric or polymerised carbohydrates or sugar alcohols or other macromolecular materials containing hydroxyl groups. Examples of suitable macromolecular materials which are insoluble, but swellable in water, are materials obtained, for example, by crosslinking any one or more of dextran, hydroxyethyl dextran, carboxymethyl dextran, sulphopropyl dextran, diethyl-aminoethyl dextran, hydroxyethyl cellulose, carboxymethyl cellulose, starch, hydroxyethyl

starch, carboxymethyl starch, any other polysaccharides and polysaccharide derivative, polyvinyl alcohol, saccharose, sorbitol and mannitol in alkaline aqueous solution by means of

- (a) an at least bifunctional bridge-forming substance of the general formula I or II

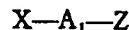


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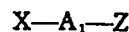


- wherein each of X, Y and Z, which may be the same or different, represents a halogen atom, preferably a chlorine or bromine atom, and each of A₁ and A₂ which may be the same or different, represents a straight or branched aliphatic saturated hydrocarbon chain substituted by one or more hydroxyl groups and preferably containing 3 to 20 carbon atoms, preferably 3 to 10 carbon atoms, said chain being optionally interrupted by one or more oxygen atoms, or
- (b) a corresponding epoxide compound obtainable by splitting off hydrogen halide from a compound of the general formula I or II.

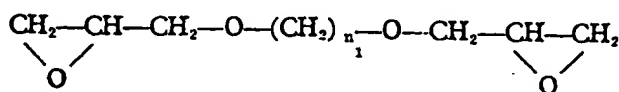
As examples of bifunctional substances of the formula



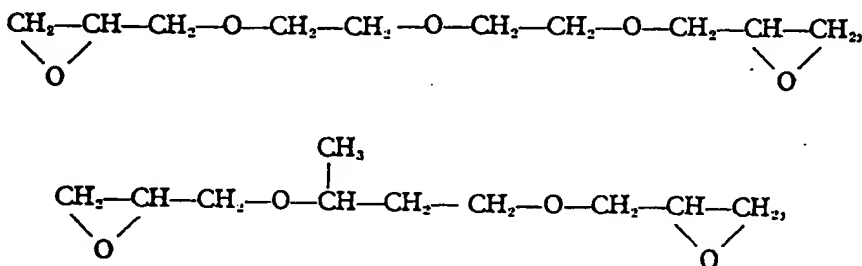
and corresponding epoxide compounds obtainable from

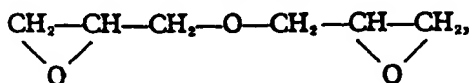


by splitting off a hydrogen halide there may be mentioned:

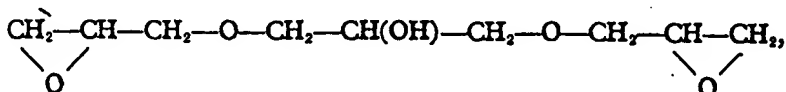


wherein n₁ represents an integer from 2 to 4,





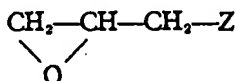
and



5 corresponding halohydrins, bifunctional glycerol derivatives of the formula

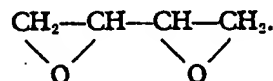


10 wherein X and Z have the meanings given above, (for example, dichlorohydrin and dibromohydrin) or corresponding epoxide compounds of the formula

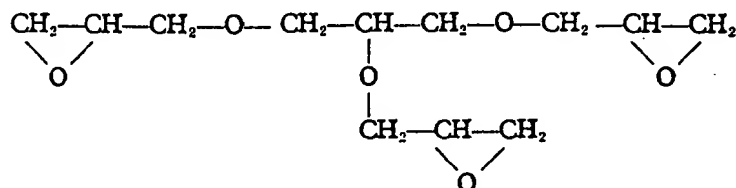


wherein Z has the meaning given above (for example epichlorohydrin and epibromohydrin) obtainable by splitting off hydrogen halide is

15 from the bifunctional bridge-forming compound is 1,2-3,4 - diepoxybutane of the formula



An example of trifunctional bridge-forming epoxide compounds corresponding to compounds of the formula



25 The water-soluble starting material is reacted with a sufficient quantity of a bridge-forming substance which is at least bifunctional to form a water-insoluble gel, i.e. a practically infinite three-dimensional network. Thus, the afore-mentioned water-soluble hydroxyl group-containing substances can be reacted in alkaline aqueous solution with one of the aforementioned bridge-forming substances in a quantity such that a gel which is insoluble in water, but capable of undergoing swelling therein is formed by crosslinking of the polymer chains. (Diepoxides and corresponding halohydrins react, for example, with hydroxyl groups to form ether bonds). The afore-mentioned bridge-forming substances have the advantage that hydroxyl groups are introduced into the bridges, thereby introducing additional hydrophilic groups into the three-dimensional network. Other hydrophilic groups, for example carboxyl groups, sulfonic acid groups, amino groups or further hydroxyl groups, can also be introduced into the hydroxyl group-containing three-dimensional network by substitution.

50 In accordance with the invention, a macromolecular product capable of being slowly broken down enzymatically to water-soluble

fragments may also be used. Thus, for example, it is possible to use starch, hydroxyethyl starch, carboxymethyl starch, or other starch derivative which has been crosslinked in the aforementioned manner by a bridge-forming agent which is at least bifunctional, the degree of total substitution for the starch being selected so that α -amylase is able to break glucosidic linkages in the three-dimensional network to such an extent that, if the gel particles are not removed after the cleansing process, they gradually disappear as water-soluble fragments as a result of the influence of α -amylase in the aqueous body fluid.

In accordance with the invention, the dry particles advantageously have an average particle size within the range of 10-1000 μ , preferably 20-500 μ , especially 30-400 μ , and more particularly 50-300 μ . The particle size can be selected, *inter alia*, by considering the desired size of the space between the particles. This space should preferably be selected so that the aqueous fluid rises up between the grains by capillary action. At the same time, the space should preferably be sufficiently large to allow bacteria and the like to pass between the particles. In select-

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ing the particle size consideration may also be given to the removal of the particles from the area of application. Thus, large particles may be selected when these may be more readily removed from the discharging surface.

In accordance with the invention the macromolecular material may be used in the form of spherical particles (e.g. obtained by so-called bead polymerisation processes) or particles having irregular configuration (e.g. obtained by so-called bulk polymerisation and grinding). Examples of some macromolecular materials which can be used according to the invention provided that they have the required swelling properties are found in British Patent Specification Nos. 854,715; 936,039; 974,054; and 1,013,585.

The preparations of the invention may contain the macromolecular material in the form of a coherent layer and may be applied to the discharging skin surface, wound or mucous membrane surface in such a manner as to enable the aqueous fluid on said surface to be absorbed by the material, whereafter the layer of material with fluid absorbed therein is removed from said surface. The process can be repeated one or more times until the desired degree of cleaning is obtained.

The carrier used in the preparation of the invention may be selected from inert fillers and other dermatologically acceptable additives, for example soap, invert soap and other conventional skin cleansing agents. Perfumes, wetting agents and disinfectants may also be used.

As mentioned above, the invention also includes a pack which contains the macromolecular material and one or more protective layers for retaining the macromolecular material when it is applied to a wound. Thus, such a pack may advantageously be used when it is desired to apply a layer of the macromolecular material to a wound surface and to fix it more effectively to the application site by covering the layer with such an associated protective layer, for example, a film of an elastic plastic material, which film is preferably provided with small openings to admit breathing to a certain degree.

Similarly, for cleansing legsores a pack in accordance with the invention contains a protective layer in the form of a plastic tube which can be inserted over the leg portion in question. The tube is then tightened below as well as above the legsores, the space between the tube and the leg being filled with the polymer particles.

The pack in accordance with the invention may also comprise a package which contains the macromolecular material and means for spraying or painting a film-forming liquid dressing over the macromolecular material or layer. Especially for the purpose of cleansing

wounds on hands and feet, the pack may be a bag containing the macromolecular material which can be used as a bandage.

According to a further embodiment of the invention, the material may be mixed with, or incorporated in, different inert materials to form, for example, dressings or bandages. Thus, for example, particles may be mixed in dry or wet condition with different fibrous materials. Suitable fibrous materials are, for example, cellulose fibres or paper pulp. Cotton fibres, the length of which can be chosen having regard to the desired use, may also be mixed with the particles. The weight proportion between particles and fibrous material can be varied within broad limits, for example between 5:1 and 1:5. If the polymer particles are mixed in wet condition with the fibre materials, the obtained wet mass is preferably formed to a sheet and the sheet is then dried.

The material used in accordance with the invention, and any additive, for example fibres, can also be mixed with dermatologically acceptable binders, for example polyethylene glycols, carboxymethyl cellulose or gum arabic. These binders are preferably selected so that the mixture obtained will get a consistency and adherence suitable for administration on the body surface, whereby the particle layer remains on the surface. The mixture may suitably have the form of an ointment. If necessary, this consistency may be obtained by mixing the particles with different binders, such as polyethylene glycols having different molecular weights.

According to a further embodiment of the invention, the material, optionally with additives, may be enclosed between thin permeable support layers of, for example, paper, cotton fabric or an inert plastics material. In this connection, the fabric must, of course, have such a mesh size that particles cannot pass through the meshes. Instead of fabrics thin films of tissue-acceptable plastics (for example polyethylene, polypropylene or polyvinyl chloride) may be used, said films being permeable, optionally through small openings, to liquids and gases. Bandages having particles enclosed between support layers, are suitably divided into a plurality of small sections, for example, in the form of a diamond pattern, to impart a higher rigidity to the bandage. The two support layers can be of the same material or different materials. In addition to the material, the bandages may comprise dermatologically acceptable additives as discussed above. The material may also be incorporated in different porous foamy tissue-acceptable materials, for example gelatin foam.

In many cases, it is desirable that the material be sterile. This can be attained in different ways, for example, by heat sterilization, sterilization by gamma irradiation or

by treatment with agents capable of killing microorganisms.

In the following Examples, Examples 1 to 3 exemplify materials suitable for use in the packs in accordance with the invention, and Examples 4 to 6 illustrate the invention.

Example 1

After having undergone an operation a 27 year old woman had a large (5×5 cm) infected sore on her left foot. The sore discharged a nasty-smelling liquid. Bacteriological tests showed a pronounced growth of *S. aureus*. For the purpose of cleansing the sore, there was applied directly thereto a layer of substantially dry water-insoluble particles of dextran crosslinked with epichlorohydrin (the reaction having been effected in alkaline aqueous solution, cf. British Patent No. 974,054) in a quantity of 1 g of sterile dry particles per 5 cm² of sore surface. The swellability of the particles was such that 1 g of dry substance absorbed 2.5 g of water. The average particle size was approximately 200 μ .

The sore with the crosslinked dextran particles applied thereon was covered with a sterile gauze bandage. The layer of particles was examined after 6 hours and it was found that the particles had been converted to a slightly yellow gel containing discharged fluid, absorbed from the sore. The particles had no smell. The gel particles were removed from the sore by means of a plastic spatula. Remaining gel particles were washed from the sore with physiological saline solution. The treatment was repeated at 12 hourly intervals. After 24 hours the sore was found to be clinically clean. No signs of infection could be clinically observed. The sore presented a healthy granulation surface at its bottom and was odourless. Cultures from the sore showed only a very slight growth of *S. aureus*. After two days, no bacteria could be found. The test was repeated for 5 days, without any complications being observed. As the sore dried up, the quantity of particle mass required progressively decreased. On the 5th day, the sore was found to be 4.5×4.5 cm in size. On the sixth day the epitel defect was covered with a pork-skin graft, which healed without difficulty and within a normal time period.

Example 2

A man, 50 years of age, had suffered for five years from bad circulation in the lower part of his left leg as a result of constrictions in the leg artery, and had suffered for one month from an infected and extremely painful sore on his left toe. The sore was one inch in diameter and emitted a discharge. Using the same technique as that described with reference to Example 1, the surface of the sore was covered with water-insoluble

spherical sterile particles of diethylaminoethyl dextran, crosslinked with epichlorohydrin (cf. British Patent No. 1,013,585). The particle size was approximately 80 μ . The total swellability per g of the dry polymer was more than 2 and less than 10 g of water. The swelling rate of the dry particles in physiological sodium chloride solution was 0.4 g per g per 5 sec. After three days, the sore was found to be completely dry and no discharge could be seen. Neither could any signs of infection be determined clinically. The pain experienced by the patient progressively decreased during the treatment period.

Example 3

A two year old boy was inadvertently scalded with boiling water on his chest over an area corresponding to twice the size of the palm of an adult hand. After three hours, serious blisters were observed to have formed on the area of the burn. The blisters were punctured and the burned surface covered with a layer of dry spherical particles consisting of crosslinked starch prepared as indicated below. The particle layer was covered with a thin foil of plasticised PVC (Gladpack, Union Carbide). The mass of swollen gel particles formed by the particles and the secretion from the sore was washed away four times a day, and a fresh layer of spherical particles consisting of crosslinked starch being applied to the scalded area together with the covering PVC foil after each washing operation. The patient suffered no pain whatsoever during the treatment process or when the bandages were changed. The burns healed without complication in seven days, without the formation of a scab and without any sign of infection. The treated area remained pale during the whole treatment period and showed no signs of swelling.

The spherical particles used, consisting of crosslinked starch, were obtained by a dispersion polymerisation technique in accordance with the method disclosed in British Patent No. 974,054; in this method, ethylene dichloride is used as a coherent phase in the dispersion and epichlorohydrin is used as a crosslinking agent. From the spherical particles thus produced, a particle fraction having an average diameter of approximately 100 μ m was removed in the dry state by sieving. The water absorption capacity was approximately 4.5 g of water per one gram of dry crosslinked starch. The particles were sterilized by γ -radiation. The particles can be completely dissolved by prolonged contact with α -amylase in neutral aqueous solution.

Example 4

A 25 year old man totally lame from the navel downwards had suffered a pressure sore

on his right side as a result of his invalidity and his impaired sense of touch. Over a period of two months, the sore had progressively deepened and secondary infection had set in, despite intensive treatment with antibiotics, applied both locally and parenterally. Relatively large quantities of material were daily exuded by the sore cavity. The sore cavity, which had a capacity of 25 ml, was filled with particulate material consisting of dextran crosslinked with epichlorohydrin (average particle size approximately 200 μ m, swellability 2.5 g of water per 1 g of dry substance), the particles being mixed with finely-ground bleached cellulose in the ratio particle of crosslinked dextran/cellulose wadding=3:1. Over a period of 6 hours there formed a fully swollen particle mass, which could readily be removed from the sore cavity by washing the same with a 0.9 per cent solution of sodium chloride in water. The treatment was repeated four times a day, and after two days it was observed that the sore cavity was perfectly clean with healthy granulations at the bottom thereof and progressively decreasing secretion therefrom. The patient was treated in this manner for five days, whereafter the sore cavity was plugged with sodium chloride wads, which were changed once a day. The pressure sore healed spontaneously twelve days later.

Example 5

Particles produced in accordance with the invention can with advantage be incorporated in an inert material having no chromatographic effect, or only a slight effect, in an aqueous environment, for example fine paper pulp, cotton fabric and macroporous plastics. In this way it is possible to produce readily handled, flexible and soft bandages or dressings which can be readily applied to discharging and weeping skin surfaces for the purpose of cleaning the same, and which can also be readily removed.

A dressing of this nature was produced in the following manner: 4 parts by weight of dry spherical particles (consisting of dextran crosslinked with epichlorohydrin in alkaline aqueous solution and having a swellability of 2.5 g of water per 1 g of dry substance) were added under agitation to 2 parts by weight of bleached fine paper pulp suspended in water. The mixture was stirred strongly with a magnet agitator for 30 minutes, whereafter the mixture was introduced into a Büchner-funnel to which was connected, for 12 hours, a zone of pressure below ambient pressure. A dressing was obtained which could readily be removed from the glass surface and which could be subsequently dried in a heating cabinet at 60°C for 12 hours. The dressing was examined under a microscope. It was observed that the fibres of the paper pulp had been uniformly distributed between the

spherical particles. Thus, a flexible, soft, light elastic material was obtained from which pieces could be readily punched and clipped in the desired size. The dressing was also found to possess good tensile strength properties, which could be further enhanced by mixing an inert binder with it. In a similar manner, dressings were prepared with the following mixing ratios: 3 g paper pulp/3 g macromolecular material, 4 g pulp/2 g macromolecular material, 4 g pulp/1 g macromolecular material, 2 g pulp/4 g macromolecular material, and 1 g pulp/4 g macromolecular material.

Upon saturating a dry dressing prepared in the above manner with water, a mass possessing suitable chromatographic properties was obtained. It was possible to show the properties in the following manner. To a dry dressing produced in accordance with the above and admixed with 25% by weight of fine paper pulp there was added 25 μ l of an albumin glycine solution. The sample was absorbed in the dressing immediately, and 4 ml of a physiologically acceptable sodium chloride solution was pipetted immediately thereafter onto the place where the sample was applied. As the dressing was converted to the gel form, the albumin was separated from the low molecular weight glycine, which latter was able to penetrate the three-dimensional network of the particles. Upon subsequent staining it could be established that the albumin fraction had been separated from the glycine centripetally.

A dry dressing produced in accordance with the above method containing paper pulp and macromolecular material in a ratio of 1:3 was applied by means of surgical tape to a dirty, infected and weeping sore. The sore had appeared one week previously as the result of a skin burn and secondary infection had set in. The secondary infection was serious and the sore painful. The dressing was changed four times a day for two days, whereafter it could be observed that the surface of the sore was perfectly clean with healthy granulation development. The sore was painless and less discharge was observed. The sore could then be transplanted, and the transplant healed without being rejected. The patient experienced no pain when the dressings were changed.

Example 6

An ointment was made up from the following ingredients:

Polyethyleneglycol having an average molecular weight of about 300 (Macrogol 300)	14.3%	
Polyethyleneglycol having an average molecular weight of about 1500 (Macrogol 1540)	28.6%	
Dry particles of crosslinked dextran		

- 5 having an average particle size of about 200 μ m and a swellability in water of 2.5 g of water per gram of dry substance (prepared according to British patent No. 974,054 by crosslinking dextran with epichlorohydrin in alkaline solution)

57.1%

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100.0%
by weight

- 15 The two polyethylene glycol products were first molten together to form a melt whereupon the dry particles of crosslinked dextran were added to the melt with stirring. The mixture was then cooled to about 20°C.

- 20 When applied to fluid discharging wounds the obtained ointment presented an excellent adherence to the skin. It absorbed the fluid on the skin and had a good cleaning effect.
- 25 In a manner similar to that described in the above Examples 1-5, usable dry particles of other macromolecular products having the required properties can be obtained for example by crosslinking dextran, carboxymethyl dextran (the carboxyl groups being in the form of the Na-salt), 3 - sulphopropyl dextran (in the form of the Na-salt), diethylaminoethyl dextran (in the form of the HCl-salt), or starch or hydroxyethyl starch or carboxymethyl starch with 1,4 - butanedioldiglycid ether or other diepoxides.

- 30 The products substituted with ionizable groups showed a noticeable rapid swelling.

WHAT WE CLAIM IS:—

- 35 1. A preparation for treating a fluid-discharging skin surface, wound, sore or mucous membrane, which comprises substantially dry particles of a water-insoluble hydrophilic macromolecular material capable of undergoing limited swelling in the fluid to form discrete gel particles, the swellability of the macromolecular material being such that the particles can absorb low molecular weight constituents of blood plasma but cannot to any material extent absorb fibrinogen or other substances of the same or higher molecular weight, in admixture or conjunction with a dermatologically suitable carrier.
- 50 2. A preparation as claimed in claim 1, wherein the swellability of the macromolecular material is such that substances having a molecular weight greater than 270,000 cannot be absorbed by the gel particles.
- 55 3. A preparation as claimed in claim 1, wherein the swellability of the macromolecular material is such that substances having a molecular weight greater than 165,000 cannot be absorbed by the gel particles.
- 60 4. A preparation as claimed in claim 1, wherein the swellability of the macromolecular material is such that substances hav-

ing a molecular weight greater than 85,000 cannot be absorbed by the gel particles.

5. A preparation as claimed in claim 1, wherein the swellability of the macromolecular material is such that substances having a molecular weight greater than 50,000 cannot be absorbed by the gel particles.

6. A preparation as claimed in any one of claims 1 to 5, wherein the swellability of the macromolecular material is such that substances having a molecular weight up to 40,000 can be at least partially absorbed by the gel particles.

7. A preparation as claimed in any one of claims 1 to 5, wherein the swellability of the macromolecular material is such that substances having a molecular weight up to 20,000 can be at least partially absorbed by the gel particles.

8. A preparation as claimed in any one of claims 1 to 5, wherein the swellability of the macromolecular material is such that substances having a molecular weight up to 5,000 can be at least partially absorbed by the gel particles.

9. A preparation as claimed in any one of claims 1 to 8, wherein the macromolecular material contains hydroxyl groups.

10. A preparation as claimed in any one of claims 1 to 9, wherein the macromolecular material contains carboxylic acid groups.

11. A preparation as claimed in any one of claims 1 to 10, wherein the macromolecular material contains sulphonic acid groups.

12. A preparation as claimed in any one of claims 1 to 11, wherein the macromolecular material contains amino groups.

13. A preparation as claimed in any one of claims 9 to 12, wherein any or all of the carboxylic acid groups, the sulphonic acid groups and amino groups are in the form of a salt.

14. A preparation as claimed in claim 1, wherein the macromolecular material is such that one gram of the dry material can, in the presence of water, absorb at least 0.5 gram of water.

15. A preparation as claimed in claim 14, wherein at least 1 gram of water can be absorbed.

16. A preparation as claimed in claim 14 or claim 15, wherein not more than 30 grams of water is absorbed.

17. A preparation as claimed in any one of claims 1 to 8 wherein the macromolecular material comprises dextran and/or carboxymethyl-dextran, crosslinked by means of epichlorohydrin in alkaline aqueous solution, and is such that one gram of dry material can, in the presence of water, absorb 1.5 to 10 grams of water.

18. A preparation as claimed in claim 17, wherein 2 to 5 grams of water can be absorbed.

19. A preparation as claimed in any one

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of claims 1 to 18, wherein the swelling rate of the macromolecular material in physiological saline solution or in water is such that one gram of dry particles absorbs in 5

5 seconds at least 0.02 gram of water.
20. A preparation as claimed in claim 19, wherein at least 0.5 gram of water is absorbed in 5 seconds.

21. A preparation as claimed in claim 19 or claim 20, wherein not more than 5 grams of water is absorbed in 5 seconds.

22. A preparation as claimed in any one of claims 19 to 21, wherein not more than 2 grams of water is absorbed in 5 seconds.

23. A preparation as claimed in any one of claims 1 to 22, wherein the macromolecular material comprises a three-dimensional network held together by bonds of a covalent nature.

24. A preparation as claimed in any one of claims 1 to 23, wherein the macromolecular material contains hydroxyl groups and comprises chains crosslinked by bridges bound to the chains by ether linkages.

25. A preparation as claimed in claim 24, wherein each bridge comprises a straight or branched aliphatic hydrocarbon chain substituted by one or more hydroxyl groups and containing 3 to 20 carbon atoms, the chain optionally being interrupted by one or more oxygen atoms.

26. A preparation as claimed in claim 25, wherein the chain contains up to 10 carbon atoms.

27. A preparation as claimed in any one of claims 24 to 26, wherein the macromolecular material, when in a fully water-swollen state, contains at least 40% by weight of water.

28. A preparation as claimed in any one of claims 24 to 26, wherein the macromolecular material, when in a fully water-swollen state, contains at least 50% by weight of water.

29. A preparation as claimed in any one of claims 1 to 22, wherein the macromolecular material is a crosslinked material comprising carbohydrate structural units.

30. A preparation as claimed in any one of claims 1 to 22, wherein the macromolecular material comprises any one or more of dextran, hydroxyethyl dextran, carboxymethyl dextran, sulphopropyl dextran, diethylaminoethyl dextran, hydroxyethyl cellulose, carboxymethyl cellulose, starch, hydroxyethyl starch, carboxymethyl starch, polyvinyl alcohol, saccharose, sorbitol and mannitol crosslinked in alkaline aqueous solution by means of

60 (a) an at least bifunctional bridge-forming substance of the general formula I or II



and



wherein each of X, Y and Z, which may be the same or different, represents a halogen atom, and each of A₁ and A₂, which may be the same or different, represents a straight or branched aliphatic, saturated hydrocarbon chain substituted by one or more hydroxyl groups said chain being optionally interrupted by one or more oxygen atoms, or

(b) a corresponding epoxide compound of the general formula I or II.

31. A preparation as claimed in claim 30, wherein the bridge-forming substance is any one of those specifically mentioned herein.

32. A preparation as claimed in claim 1, wherein the macromolecular material is any one of those specifically mentioned herein.

33. A preparation as claimed in any one of claims 1 to 29, wherein the macromolecular material is capable of being broken down enzymatically to water-soluble fragments.

34. A preparation as claimed in any one of claims 1 to 33, wherein the substantially dry particles of macromolecular material have an average particle size of from 10 to 1,000 μ .

35. A preparation as claimed in claim 34, wherein the average particle size is 30 to 400 μ .

36. A preparation as claimed in any one of claims 1 to 35, wherein the particles are substantially spherical.

37. A preparation as claimed in any one of claims 1 to 36, wherein the macromolecular material is in the form of a coherent layer.

38. A preparation as claimed in any one of claims 1 to 37, wherein the carrier is a binder, filler, wetting agent, disinfectant, perfume, or a mixture of any two or more of such substances.

39. A preparation as claimed in any one of claims 1 to 38, wherein the carrier comprises a fibrous material.

40. A preparation as claimed in claim 39, wherein the carrier comprises cellulose fibres or paper pulp.

41. A preparation as claimed in any one of claims 1 to 40, which is in the form of a physiologically sterile dressing or bandage.

42. A preparation as claimed in any one of claims 1 to 41, which is in the form of an ointment.

43. A preparation as claimed in claim 42, which contains as a binder one or more polyethylene glycols, carboxymethyl cellulose or gum arabic.

44. A pack for treating a fluid-discharging

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- skin surface, wound, sore or mucous membrane, which comprises a container or package containing substantially dry particles of a water-insoluble hydrophilic macromolecular material capable of undergoing limited swelling in the fluid to form discrete gel particles, the swellability of the macromolecular material being such that the particles can absorb low molecular weight constituents of blood plasma but cannot to any material extent absorb fibrinogen or other substances or the same or higher molecular weight, and also containing one or more protective layers for retaining the macromolecular material when applied to a wound.
45. A pack as claimed in claim 44, wherein the protective layer is a film of an elastic plastic material.
46. A pack as claimed in claim 44, which comprises, instead of one or more protective layers, means for spraying a film-forming liquid dressing over the macromolecular material or layer.
47. A pack as claimed in claim 44, wherein the macromolecular material is sandwiched between two permeable support layers.
48. A pack as claimed in claim 44, wherein the protective layer is a film in the form of a tube.
49. A pack as claimed in any one of claims 44, 45, 47 and 48, wherein the protective layer or layers are provided with a plurality of small openings to admit breathing.
50. A pack as claimed in any one of claims 44, 45 and 47 to 49, which is in the form of a physiologically sterile bandage.
51. A pack as claimed in any one of claims 44 to 50, wherein the macromolecular material is in admixture with or incorporated in a dermatologically suitable carrier.
52. A pack as claimed in claim 51, wherein the carrier is as specified in any one of claims 38 to 40.
53. A pack as claimed in any one of claims 44 to 52, wherein the macromolecular material is as specified in any one of claims 2 to 37.
54. A preparation as claimed in claim 1 or claim 44, substantially as described in any one of Examples 4 to 6 herein.

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